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# MHC Class I Molecules and Progression to AIDS

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limited to patients with tumors 5 cm or less in diameter, long-term survival approaches 75 percent at four years, whereas transplantation in those with tumors larger than 5 cm has been associated with less than 30 percent survival.<sup>2,3</sup> These data led to the exclusion of patients with larger tumors from the waiting list for cadaveric organs. We suggest that if the supply of cadaveric organs were to exceed the current demand, patients with the worst outcomes would be considered candidates. Can we now refuse to offer these patients transplantation when a healthy living donor provides the graft?

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The authors reply:

*To the Editor:* We agree with most of the views of Miller and Delmonico, including their conclusions that the “transplantation community . . . does indeed monitor itself” and that it shows “concern for the well-being of living donors.”<sup>1,2</sup> In our article, we never question this commitment. We also agree that the surgical model of innovation based on professional self-regulation rather than administrative regulation has proved to be an extremely effective way to advance the field of surgery to benefit patients.

Our disagreement with Miller and Delmonico focuses on whether the professional regulatory model involving conferences, colloquiums, and position papers will prove adequate for dealing with the transplantation of liver grafts from adult living donors and for protecting potential donors. We believe that the best way to optimize the use of this innovative technology is to define clearly the experimental protocol, standardize the operation, ensure the “field strength” of the surgical team, and record and share all data on outcomes (including program-specific data) with the professional community and with patients. If the professional community can accomplish these tasks quickly — and thus far they have not — there may not be a need for formal regulatory control.

Shaked and Lucey highlight an unresolved issue with regard to recipients. Since the four-year survival among patients who have hepatocellular carcinomas larger than 5 cm and undergo transplantation is so poor,<sup>3</sup> this group has been excluded from the waiting list for cadaveric organs. Shaked and Lucey suggest that living donors be subjected to complications and possibly death to provide grafts to recipients with hepatocellular carcinomas, even though the transplantation community has declined to use cadaveric grafts in such

patients. In our article, we refer to the need to balance the short-term and long-term risks to the donor with the potential benefits to the recipient. The proposal offered by Shaked and Lucey demonstrates the need for the transplantation community to specify what outcomes in a recipient are acceptable before a living donor is subjected to surgical risk. It also raises the question of whether individual programs can be required to comply with standards established by the surgical transplantation community through professional self-regulation.

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## MHC Class I Molecules and Progression to AIDS

*To the Editor:* Gao et al. (May 31 issue)<sup>1</sup> report the identification of specific HLA-B\*35-Px subtypes as responsible for the association between HLA-B\*35 and rapid progression to AIDS, and they stress the importance of homozygosity for HLA-B\*35 as a predictor of even more rapid progression. Their extensive analysis confirms the known protective effect of the HLA-B\*27 and B\*57 subtypes against progression to AIDS, at least in whites.<sup>2</sup>

Unlike Gao and colleagues, we think that there is an important influence of numerous major-histocompatibility-complex (MHC) gene products. The A1,B8,DR3 haplotype, for instance, has repeatedly been shown to be associated with fast progression to human immunodeficiency virus (HIV) disease and rapid loss of CD4 T cells,<sup>3,4</sup> and several other HLA haplotypes can predict disease progression.<sup>2</sup> Caution should be exercised before early, aggressive antiretroviral therapy is recommended for HLA-B\*35-positive patients. We have been following an HIV-infected woman without symptoms since her seroconversion in 1991 (she is now 37 years old). She has never received antiretroviral therapy and still has a high CD4 cell count (606 per cubic millimeter, 36.6 percent of total lymphocytes) and CD4:CD8 ratio (0.91), despite being homozygous for HLA-B\*35. Perhaps the presence of HLA A2,A26 alleles in her haplotype counteracts the effects of HLA-B\*35, since A2 is common in frequently exposed HIV-seronegative persons<sup>5</sup> and A26 may confer resistance to the progression of HIV disease.<sup>2</sup>

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The authors reply:

*To the Editor:* To date, over 50 papers have been published that attempt to associate HLA haplotypes with the rate of progression to AIDS. Because of low statistical power and small samples, the results of many cannot be considered rigorously validated. Among the strongest associations are the influence of HLA class I homozygosity and the codominant influence of HLA-B\*35. The goal of our recent report was to demonstrate that the previously reported effect of B\*35<sup>1</sup> could be connected directly to the peptide-binding specificity of certain HLA-B\*35 subtypes. We are, of course, aware of several other genetic factors that mitigate progression to AIDS, including the genes encoding CC chemokine receptors 5 and 2, interleukin-10, and stromal-cell–derived factor 1 as well as other HLA alleles, and we described them in our cohorts.<sup>1,2</sup> These factors may counteract each other, which could be the case for the HLA-B\*35–homozygous woman described by Cainelli et al. This patient's AIDS-free survival for 10 years is remarkable. In our experience with six patients homozygous for HLA-B\*35 in five cohorts, five progressed to an AIDS-defining condition in less than 6 years and the other one in less than 10 years.

We agree that multiple genetic and viral influences should be considered when a therapeutic regimen for an HIV-

infected patient is chosen. We believe that B\*35-Px is one of the more influential factors.

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### Spirolactone in Addition to ACE Inhibition to Reduce Proteinuria in Patients with Chronic Renal Disease

*To the Editor:* Angiotensin-converting–enzyme (ACE) inhibitors have been shown to reduce proteinuria and slow the progression of renal disease.<sup>1</sup> Although to date angiotensin II has been the focus of attention as the primary mediator of the renin–angiotensin–aldosterone system, several studies have raised the possibility that aldosterone itself has a role in mediating progressive renal disease.<sup>2,3</sup> Pitt et al.<sup>4</sup> showed that blockade of aldosterone receptors by spironolactone significantly reduced the risk of morbidity and death among patients with heart failure who were already receiving ACE inhibitors. The authors hypothesized that the benefits were not due to the hemodynamic effects of spironolactone but, instead, may have been due to an adverse effect of aldosterone on myocardial and vascular smooth-muscle cells. We tested the hypothesis that spironolactone may act along with ACE inhibitors in the kidney to reduce proteinuria.

TABLE 1. CLINICAL CHARACTERISTICS AND FINDINGS BEFORE AND AFTER TREATMENT WITH SPIRONOLACTONE IN EIGHT PATIENTS.

SEX	AGE	URINARY PROTEIN		CREATININE CLEARANCE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		DIAGNOSIS
		BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
	yr	g/day		ml/sec		mm/Hg				
Male	62	2.87	0.94	1.30	0.66	120	120	80	70	Type 2 diabetes
Male	60	8.90	3.30	0.58	0.59	120	110	80	70	Type 2 diabetes
Female	43	2.83	2.94	2.50	2.02	120	110	90	70	Systemic lupus erythematosus
Male	71	3.00	1.80	0.62	0.45	200	170	100	90	Type 2 diabetes
Male	55	2.21	0.86	2.40	3.90	170	130	90	80	Type 2 diabetes
Male	74	6.17	2.02	1.24	1.30	120	130	90	80	Focal sclerosis with segmental hyalinosis
Male	61	1.17	0.36	1.71	1.51	140	160	90	70	Type 2 diabetes
Female	31	3.30	1.75	0.48	0.53	120	115	90	80	Vasculitis
Mean ±SD*		3.81±2.50	1.75±1.02	1.35±0.80	1.37±1.17	138.8±30.4	130.6±22.7	88.8±6.4	76.3±7.4	

\*P<0.02 for the comparison between pretreatment and post-treatment urinary protein, by the paired t-test. There were no other significant differences between pretreatment and post-treatment values.